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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/437,458	11/10/99	GIORDANO	A	50093/014001

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EXAMINER	
LEFFERS JR,G	
ART UNIT	**PAPER NUMBER**
1636	8

DATE MAILED: 02/13/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/437,458	Giordano, et al.
Examiner	**Group Art Unit**
Gerald G. Leffers Jr.	1636

☒ Responsive to communication(s) filed on *Nov 24, 2000*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *THREE* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-3 and 12-31* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3 and 12-31* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Receipt is acknowledged of applicants' amendment, filed 11/24/00 as Paper No. 7, in which the claims 1-2 were amended, claims 4-11 were canceled and new claims 12-31 were added. Receipt is also acknowledged of an Information Disclosure Statement, filed 7/13/00. The signed and initialed PTO 1449 has been mailed along with this action.

Applicant's election without traverse of Group I (claims 1-3), and the species of SEQ ID NO: 20, in Paper No. 7 is acknowledged. Claims 1-3 and 12-31 are pending in this application.

Any objection or rejection made in the action mailed 5/23/00 has been withdrawn. Because each of the new rejections made in this action were necessitated by Applicants' amendment, this action is FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 12-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had

possession of the claimed invention. **This rejection is maintained for reasons of record in Paper No. 5, mailed 5/23/00 and repeated below.**

Claims 1-3 and 12-31 are drawn toward a nucleic acid sequence comprising any one of the nucleic acid sequences of SEQ ID NOS: 1-20, or a subfragment derivative thereof, wherein an mRNA molecule comprising the derived sequence has an RNA binding protein (RBP) binding activity or has an altered or regulated functionality. Claim 3 and specification disclose that the term "regulation of mRNA functionality" comprises an alteration in pre-mRNA processing or in the stabilization, translational efficiency, localization, sequestration, editing, or splicing functions of said mRNA. As written the claims use open claim language that encompasses any nucleic acid which might contain a derivative of one of SEQ ID NOS: 1-20, including genomic DNA sequences, full open reading frames, fusion constructs, etc. Moreover, the claim is also extremely broad in that it encompasses "subfragments" of unspecified length relative to the parental sequence which are "derived" from SEQ ID NOS: 1-20. The claims and specification do not specify how much of the parental sequence is required in order to constitute a "derivative" of one of SEQ ID NOS: 1-20. Claims 1-3 are thus very broad genus claims.

In the specification, SEQ ID NOS: 1-20 are described as being identified as untranslated RNA sequences from the known sequences (obtained from public databases) of biologically important genes and which have specific RBP-binding activity (page 10, line 7). The specification does not disclose which RBPs are in fact bound by any one of the identified sequences. The specification does not disclose for any one of SEQ ID NOS: 1-20 where it is

located within the context of the gene with which it is associated. The specification does not disclose whether any one of SEQ ID NOS: 1-20 affects the functional characteristics of the mRNA with which it is associated. The specification does not disclose a common structural feature among the sequences identified in SEQ ID NOS: 1-20, nor does it disclose a common structural feature for the "derivatives" of any one of SEQ ID NOS: 1-20. There is no guidance in the specification as to what may be the "optimized" sequences for any one of SEQ ID NOS: 1-20 and no relevant examples in which the specified sequences have been "optimized".

Because the claimed genus is extremely broad, because there is no disclosure in the specification as to which portions of SEQ ID NOS: 1-20 bind RBPs and no relevant example of where one of the identified sequences has been used to bind an RBP or alter an mRNAs' functional characteristics and because one cannot predict based on the teachings of the specification or the prior art as to what changes in one of SEQ ID NOS: 1-20 will allow binding of an RBP or allow regulation of an mRNAs' functional characteristics, one of skill in the art would not be able to visualize a representative number of all of the nucleic acids encompassed by claims 1-3. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicants were not in possession of the claimed inventions.

Response to Arguments

Applicant's arguments filed 11/24/00 have been fully considered but they are not persuasive. Applicants' response essentially argues that: 1) the specification teaches on page 10-

12 that each of the nucleic acids recited in SEQ ID NOS: 1-20 has RBP binding activity, 2) any heterologous nucleic acid sequence containing the sequence of any one of SEQ ID NOS: 1-20 also has RBP binding activity, 3) the specification and prior art provide methods for identifying subfragments of each of SEQ ID NOS: 1-20 which have RBP activity or the ability to regulate RNA functionality, and 4) the specification provides a number of distinguishing identifying characteristics of a nucleic acid subfragment, including the functional characteristics of the subfragments, methods of making the subfragments and the parent sequences from which the subfragments are defined.

The specification does teach that a nucleotide sequence comprising each of the SEQ ID NOS: 1-20 does have RBP-binding activity. However, it is not clear as to whether the gel retardation activity or filter-binding activity seen for the nucleic acids described by SEQ ID NOS: 1-20 were limited to SEQ ID NOS: 1-20 or to larger nucleic acids comprising these sequences. There is no description within the specification as to which portions of any one of SEQ ID NOS: 1-20 are important for the observed RBP-binding activity, nor is there a description of such RBP-binding activity for any of the very large number of embodiments wherein a subfragment of the recited sequences is attached to a heterologous nucleic acid sequence. For example, SEQ ID NO: 20 is 259 nucleotides long. Even with the limitation of a subfragment generated by deletion at the 3' or 5' end, or by internal deletion, an enormous number of subfragments are possible. There is no description of what RBPs are bound by any of the claimed sequences such that one could envision what subsequences are important for the observed RBP-binding activity based on

similar interactions with different nucleic acid sequences (i.e. recognition of a common binding motif such as for RBPs involved in transcript stability or translation).

The assertion that any heterologous nucleic acid sequence comprising the full nucleotide sequence described by SEQ ID NO: 1-20 would necessarily bind an RBP or regulate the functionality of an mRNA sequence to which it was attached is inaccurate. RNA folding, like the folding of a polypeptide, is a largely unpredictable process. One of skill in the art would reasonably expect that the presence of an operatively linked RNA sequence would affect the tertiary structure of the claimed sequence, and thus, its ability to bind the RBP. While there are computer algorithms available for prediction of an RNA structure, they are not infallible and this unpredictability is further offset by the lack of any functional characterization of the claimed nucleic acid sequences other than in a "blind" filter-binding or gel-retardation assay wherein the character of the nucleic acid sequence bound by protein(s), or of the protein(s) which bind the nucleic acid sequence. For example, even if one had a predictable structure for one of the claimed UTR sequences by itself, one would not know which regions are necessary for the observed RBP-binding activity. Without such knowledge, one would necessarily be unable to predict which structures affected by the presence of a heterologous nucleic acid would be dispensable for RBP-binding activity or functionality of an mRNA comprising that sequence.

The assertion that the specification provides methods for identifying subfragments of each of SEQ ID NOS: 1-20 which have RBP-binding activity or which regulate functionality of an mRNA to which they are attached appears to be an argument more appropriate to issues of

enablement. The issue here is whether a representative number of embodiments of the very large claimed genus have been described. They have not.

The assertion that the specification provides a number of distinguishing identifying characteristics of a nucleic acid subfragment of the invention, including functional characteristics of the subfragments, methods of making such subfragments and the parent sequences from which they are derived again argues enablement as well as inaccurately asserting that a representative number of embodiments have been described. As noted above, there is no structural characterization for any one of the claimed sequences linked to RBP-binding function for any of the species encompassed by the claimed genus, except for a barely described experiment in which a nucleic acid sequence comprising one of SEQ ID NOS: 1-20 was shown to bind protein by a gel-retardation or filter-binding assay. There is no link to a specific protein and no description as to which structures within the specified UTR are required for binding and no basis provided for one of skill in the art to determine such sequences short of actual experimentation.

While the specification may be enabling for determination of the claimed sequences which retain RBP-binding activity, it does not provide enough description of the structural/functional characteristics for any of the sequences for which it presents data to allow one of skill in the art to extrapolate that data to a representative number of embodiments for the genus of the entire sequence linked to any heterologous sequence, much less the more broadly claimed genus of subfragments operatively linked to any heterologous sequence.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 and 12-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is a new rejection necessitated by applicants' amendment filed 11/24/00.**

Claim 1 is vague and indefinite in that it specifies an isolated nucleic acid wherein the nucleic acid is part of a larger nucleic acid sequence. This makes the claim unclear as to whether the claim is directed only to that first nucleic acid or only to the larger nucleic acid which it is a part of, or to both nucleic acids. It appears from reading the specification that the invention is the combination of the heterologous sequence and the first nucleic acid sequence. Therefore, it would be remedial to amend the claim language to clearly read on the larger nucleic acid comprising the first nucleic acid which confers RBP-binding activity or functionality on the larger molecule.

Claim 1 is also vague and indefinite in that the metes and bounds of the phrase "..wherein an mRNA molecule comprising said nucleic acid, or an mRNA comprising said subfragment nucleic acid has RNA binding protein (RBP) binding activity or regulates the functionality of said nucleic acid." are unclear. As written, it appears the claim is directed to a nucleic acid in which the larger RNA regulates the functionality of the small nucleic acid which it comprises.

Upon reading applicants' response and the specification it appears that the claim is intended to specify the smaller nucleic acid which has RBP-binding activity regulates the functionality of the mRNA of which it is part. It would be remedial to amend the claim language to be more consistent with the invention described in the specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1, 3 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Claffey et al (Mol. Biol. Cell. Vol. 9, pages 469-481; see the entire document). **This rejection is a new rejection necessitated by applicants' amendment filed 11/24/00.**

The rejected claims encompass a subfragment of SEQ ID NO: 20 operatively linked to a heterologous polypeptide wherein the subfragment is derived by deletion from either end or internal deletion of SEQ ID NO:20. The claimed subfragment nucleic acid can, as part of a larger mRNA, demonstrate RBP-activity or a regulated functionality (e.g. pre-mRNA processing, mRNA stability, translational efficiency, etc.). The final three nucleotides of SEQ ID NO: 20 are -tag-. These nucleotides are present at ~ nt 1069 of the 3' untranslated region of an isolated

nucleotide described by Claffey et al as encoding human VPF/VEGF and which is responsible for mediating an hypoxia-induced stability for the VPF/VEGF message (Abstract; Figure 3).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be

retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald Leffers, Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on Monday through Friday, from about 9:00 AM to about 5:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

GLJ

G. Leffers, Jr.

Patent Examiner

Art Unit 1636

DAVID GUZO
PRIMARY EXAMINER

February 12, 2001

Attach paper #8
09/437,458

(FILE 'HOME' ENTERED AT 08:52:41 ON 12 FEB 2001)

FILE 'EMBASE, MEDLINE, BIOSIS, CAPLUS' ENTERED AT 08:52:52 ON 12 FEB 2001

L1	28	S	(GIORDANA, A?)/IN,AU
L2	1724	S	(GIORDANO, A?)/IN,AU
L3	737	S	(XAVIER, A?)/IN,AU
L4	2461	S	L2 OR L3
L5	0	S	L2 AND L3
L6	0	S	L4 AND MAHOGANY
L7	1	S	L4 AND UNTRANSLATED
L8	41	S	L4 AND MRNA
L9	16		DUPLICATE REMOVE L8 (25 DUPLICATES REMOVED)

Attach paper #8

EAST: DERWENT EPO JPO USPAT 09/437,458 02/11/01

L1	57	giordano-a$.in.
L2	18	xavier-a$.in.
L3	75	1 or 2
L4	0	1 and 2
L5	0	3 and mahogany
L7	2	3 and untranslated
L8	2	6 not 7
L6	4	3 and mrna
L9	7	3 and rna